PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JAB 1681-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/00276	International filing date *(day/month/year)* 13.01.2003	Priority date *(day/month/year)* 16.01.2002
International Patent Classification (IPC) or both national classification and IPC C07D405/12		
Applicant JANSSEN PHARMACEUTICA N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.06.2003	15.04.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Stellmach, J Telephone No. +49 89 2399-8279

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/00276

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-9 as originally filed

Claims, Numbers

1-8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-8
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

2. Citations and explanations

see separate sheet

SECTION V ----------

1. Prior art

Documents (1) - (11) which were cited in the International **Search Report** and the **Written Opinion** are considered to represent relevant prior art in this **Preliminary Examination Report**; the numbering will be adhered to in the rest of the procedure.

(1) WO-A-96/16 060
(2) EP-A-0 445 862
(3) EP-A-0 389 037
(4) US-A-5 374 637
(5) WO-A-96/10 027
(6) WO-A-97/31 897
(7) WO-A-97/24 356
(8) WO-A-97/30 031
(9) EP-A-0 299 566
(10) WO-A-00/30 640
(11) WO-A-00/66 170

2. Novelty

Documents (1), (10) and (11) disclose specifically the compound "**prucalopride**". Citation (2) discloses N-oxide compounds (salts) generically but none of the documents describes prucalopride N-oxide explicitly. Documents (3) - (9) disclose structurally similar piperidine compounds (analogues) and their N-oxides with the same activity (*gastrointestinal motility stimulating properties, 5-HT_4 receptor agonist, facilitation of both cholinergic and non-cholinergic excitatory neurotransmission*). With regard to the cited prior art (1) - (11) the claimed subject-matter appears to meet the requirements of novelty (**Article 33 (2) PCT**).

3. Inventive step

3.1 For the assessment of inventive step, document (1) is considered to represent the closest prior art for the claimed compounds, since this document discloses prucalopride and its addition salts (loc. cit. claims 1-3) with *gastrointestinal motility stimulating properties*. Starting from this closest prior art, the technical problem underlying the application in suit (**Article 33 (3) PCT, Rule 5.1 (a) (iii) PCT**) can be considered to be the provision of **prucalopride** salts with unexpected properties. The generic formula of

citations (2) and (3) embrace **prucalopride** and its analogues and specifically refer to the N-oxides of all claimed compounds and their preparation (see (2), page 4, lines 39-42, see (3), page 3, lines 49-51). Accordingly, for the skilled person starting from the compounds disclosed in (1) there is a clear **incentive** that for the N-oxides of the compounds the *gastrointestinal motility stimulating properties* are maintained. The skilled man, who was faced with the problem of finding further piperidine derivatives which possess *gastrointestinal motility stimulating properties* due to the structural modifications suggested in the prior art would have been able to predict with certainty the claimed salts/compounds to solve the above defined problem. Accordingly, insofar as only the above defined problem is actually solved, the requirements of **Article 33 (3) PCT** are not met.

3.2 The Applicant has performed a comparative test (see pages 8/9). In his letter of reply dated 18.12.03 the Applicant has stated that for the comparative tests "prucalopride succinate" was taken. With regard to the very small effects (see the table on page 9) additional data were presented at the end of page 2 of his letter of reply with larger effects in order to demonstrate the unexpected effects of the claimed compound/salt. Since the technical problem underlying the application is solved, the requirements of **Article 33 (3) PCT** are met.

4. Industrial applicability

No objection re industrial applicability of claims 1 - 8 arises insofar the claimed compounds exhibits the alleged unexpected pharmacological properties (**Article 33 (4) PCT**).

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